
Phase I study of IM Injection of VEGF Producing MSC for the Treatment of Critical Limb Ischemia

Grant Award Details

Phase I study of IM Injection of VEGF Producing MSC for the Treatment of Critical Limb Ischemia

Grant Type: Disease Team Therapy Planning I

Grant Number: DR2-05423

Investigator:

Name: John Laird

Institution: University of California, Davis

Type: PI

Disease Focus: Heart Disease

Award Value: \$76,066

Status: Closed

Progress Reports

Reporting Period: Year 1

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Grant Application Details

Application Title: Phase I study of IM Injection of VEGF Producing MSC for the Treatment of Critical Limb Ischemia

Public Abstract:

Critical limb ischemia (CLI) represents a significant unmet medical need without any approved medical therapies for patients who fail surgical or angioplasty procedures to restore blood flow to the lower leg. CLI affects 2 million people in the U.S. and is associated with an increased risk of leg amputation and death. Amputation rates in patients not suitable for surgery or angioplasty are reported to be up to 30-50% after 1 year. Patients who are not eligible for revascularization procedures are managed with palliative care, but would be candidates for the proposed phase I clinical trial.

In an effort to combat CLI, prior and ongoing clinical trials that our group and others have conducted have evaluated direct injection of purified growth factors into the limb that has low blood flow. Some trials have tested plasmids that would produce the blood vessel growth factors for a short period of time. These therapies did show benefit in early stage clinical trials but were not significantly better than controls in Phase III (late stage) trials, probably due to the short duration of presence of the growth factors and their inability to spread to the areas most needed. Other clinical trials ongoing in our vascular center and others are testing the patient's own stem cells, moved from the bone marrow to the damaged limb, and those studies are showing some benefit, although the final assessments are not yet completed. Stem cells can have benefit in limb ischemia because they can actively seek out areas of low oxygen and will produce some growth factors to try to encourage blood vessel growth. But in cases where the circulation needs very high levels of rescue, this strategy might not be enough.

As an improved strategy we are combining the stem cell and growth factor approaches to make a more potent therapy. We have engineered human Mesenchymal Stem Cells (MSCs) to produce high levels of the strong angiogenic agent VEGF for this novel approach (MSC/VEGF). We and others have documented over the past 20+ years that MSC are capable of sustained expression of growth factors, migrate into the areas of lowest oxygen in the tissues after injection, and wrap around the damaged or tiny blood vessels to secrete their factors where they are needed most.

These MSC/VEGF cells are highly potent, safe and effective in our preclinical studies. These human stem cells designed to produce VEGF as "paramedic delivery vehicles armed with growth factor to administer" rapidly restored blood flow to the limbs of rodents who had zero circulation in one leg. With funding that could be potentially obtained through the proposed application we will follow the detailed steps to move this candidate therapy into clinical trials, and will initiate and complete an early phase clinical trial to test safety and potential efficacy of this product that is designed to save limbs from amputation.

Statement of Benefit to California:

Critical Limb Ischemia (CLI) represents a significant unmet medical need without any curative therapies in its end stages, after even the best revascularization attempts using sophisticated catheters, stents, and bypass surgeries have failed. CLI affects over 2 million people in the US and the prevalence is increasing due to the aging of our population and the diabetes epidemic. In 2007, the treatment of diabetes and its complications in the USA generated \$116 billion in direct costs; at least 33% of these costs were linked to the treatment of ischemic foot ulcers, associated with CLI. Once a patient develops CLI in a limb, the risk of needing amputation of the other limb is 50% after 6 years, with devastating consequences. Treatment costs are immense and lives are significantly shortened by this morbid disease.

The symptoms associated with this very severe form of lower extremity peripheral artery disease (PAD) are pain in the foot at rest, non-healing ulcers, limb/digital gangrene and delayed wound healing. The quality of life for those with CLI is extremely poor and reported to be similar to that of patients with end stage malignancy. Most patients with CLI will undergo repeat hospitalizations and surgical/endovascular procedures in an effort to preserve the limb, progress to immobility and need constant care. Unfortunately, the limb salvage efforts are often not effective enough, and despite multiple attempts at revascularization, the wounds still fail to heal. The final stage in 25% of cases is limb amputation, which is associated with a high mortality rate within 6 months. Amputation rates in patients not suitable for revascularization are reported to be up to 30-50% after 1 year. Fewer than half of all CLI patients achieve full mobility after an amputation and only one in four above-the-knee amputees will ever wear a prosthesis.

Between 199– 1999, over 28,000 first time lower extremity bypass procedures were performed in California for CLI, and 29% of patients were admitted to the hospital for at least one subsequent bypass operation or revision procedure. The 5-year amputation free survival rate for this group of CLI patients from California was only 51.1%. The direct costs to California for the treatment of CLI and diabetic ischemic ulcers are substantial.

The lost ability of no-option CLI patients to remain in the CA workforce, to support their families, and to pay taxes causes additional financial strain on the state's economy. The goal of the proposed study is to develop and apply a safe and effective stem cell therapy to save limbs from amputation due to disorders of the vasculature that currently cannot be cured. The successful implementation of our planned therapies will significantly reduce the cost of healthcare in California and could bring people currently unable to work due to immobility back to the workforce and active lifestyles, with a significantly improved quality of life.

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